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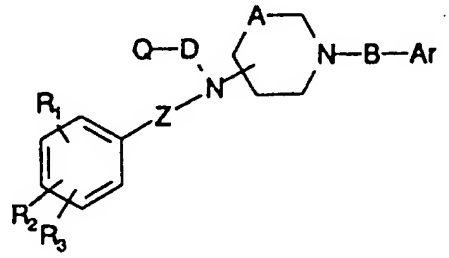
(54) Title: NOVEL COMPOUNDS

(57) Abstract

A compound of formula (I) or a salt thereof, or a solvate thereof, wherein A represents $(CH_2)_n$ wherein n represents zero or an integer 1 or 2; B represents a C_{2-4}n-alkylene group wherein each carbon is optionally substituted by a C_{1-6}alkyl group; Z represents a bond $(CH_2)_m$ wherein m is an integer in the range of from 1 to 4 or X-CH_2-CH_2 wherein X represents O or S; D represents CO, SO_2, NH-CO, NH-SO_2, -CH=CH- or P(O)OR_4 wherein R_4 is C_{1-6}alkyl; Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamide, 1-imidazo, alkyl or haloalkyl, or Q represents substituted furanyl, substituted thienyl or substituted or unsubstituted: pyranyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl, indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group; R_1, R_2 and R_3 each independently represent H, alkyl, OH or alkoxy or, if attached to adjacent carbon atoms, any two of R_1, R_2 or R_3 together with the carbon atoms to which they are attached may form a fused heterocyclic ring of four to six atoms wherein one, two or three of the said atoms are oxygen or nitrogen; and Ar represents substituted or unsubstituted aryl, wherein the optional substituents are the above defined R_1, R_2 and R_3 or Ar represents a substituted or unsubstituted heteroaryl group; a process for preparing such compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in medicine.



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Novel Compounds

The invention relates to certain novel compounds, to pharmaceutical compositions containing such compounds, to a process for the preparation of such compounds and to the use of such compounds as active therapeutic agents.

European Patent Application, Publication Number 0416581 discloses certain substituted N-benzylpiperidine amides which are stated to be useful in the treatment of cardiac arrhythmias.

Anti-arrhythmic agents are classified according to their electrophysiological effects on the cardiac cell (Vaugham-Williams, 1970, 1989) : class I agents block the fast sodium current, class II agents are beta-adrenergic blockers, class III agents block potassium currents, class IV agents block the calcium current, and class V agents are specific sinus node inhibitors.

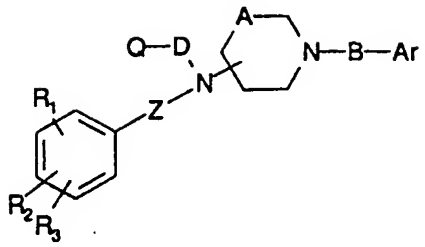
A majority of ventricular and atrial arrhythmias are related to reentrant circuit. The prolongation of myocardial refractoriness within or surrounding such a reentrant circuit is a potential mechanism for the management of cardiac arrhythmias.

Because class III antiarrhythmic agents block cardiac potassium currents, they prolong the repolarisation process and increase refractoriness. Consequently class III agents represent the most specific class to treat reentrant arrhythmias.

However, due to their mechanism of action, i.e. a concentration dependent increase in the cardiac action potential duration, higher doses of class III antiarrhythmic agents may trigger arrhythmias. Such arrhythmias, called Torsade de Pointe represent the main adverse effect for all pure class III compounds currently in development.

It has been discovered that certain novel piperidine derivatives induce a self-limiting increase of the cardiac action potential duration, related to a dual blockade of cardiac potassium and calcium channels. Consequently, they are considered to be useful anti-arrhythmic agents having an improved pharmacological profile over pure class III anti-arrhythmic agents, in particular they area considered to show a low proarrhythmic potential and readily restore the contractile function of the ischaemic myocardium. They are considered to be particularly useful for the treatment of atrial or ventricular cardiac arrhythmias.

Accordingly, the invention relates to a compound of formula (I):



(I)

or a salt thereof, or a solvate thereof, wherein

A represents $(CH_2)_n$ wherein n represents zero or an integer 1 or 2;

B represents a C_{2-4} n-alkylene group wherein each carbon is optionally substituted by a C_{1-6} alkyl group;

Z represents a bond $(CH_2)_m$ wherein m is an integer in the range of form 1 to 4 or X-CH_2-CH_2 wherein X represents O or S;

D represents CO, SO_2, NH-CO, NH-SO_2, -CH=CH- or P(O)OR_4 wherein R_4 is C_{1-6} alkyl;

Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamide, 1-imidazo, alkyl or haloalkyl, or Q represents substituted furanyl, substituted thienyl or substituted or unsubstituted: pyranyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl, indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group;

R_1, R_2 and R_3 each independently represent H, alkyl, OH or alkoxy or, if attached to adjacent carbon atoms, any two of R_1, R_2 or R_3 together with the carbon atoms to which they are attached may form a fused heterocyclic ring of four to six atoms wherein one, two or three of the said atoms are oxygen or nitrogen; and

Ar represents substituted or unsubstituted aryl, wherein the optional substituents are the above defined R_1, R_2 and R_3 or Ar represents a substituted or unsubstituted heteroaryl group.

Suitably, A represents CH_2.

Suitably, B represents an unsubstituted C_{2-4} n-alkylene group.

Preferably, B represents CH_2CH_2.

Suitably, Z represents a bond, $(CH_2)_m$ wherein m is an integer in the range of from 1 to 4, preferably m is 1, or 2.

Favourably, Z represents a bond, CH_2 or $(CH_2)_2$, preferably a bond.

Suitably, D represents CO, SO_2, NH-CO or -CH=CH-, preferably CO.

Suitably, Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5, suitably 1 to 3, substituents selected from the list consisting of nitro, halogen, alkylsulfonamido, 1-imidazo, alkyl or haloalkyl, favourably nitro, halogen or alkylsulphonylamido, preferably nitro.

Suitably, Q represents substituted furanyl, substituted thienyl or substituted or unsubstituted: pyranyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl; indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group.

Favourably, Q represents aryl.

Favourably, Q represents substituted thienyl or substituted or unsubstituted: pyranyl.

Favourably, Q represents the benzo fused equivalents of furanyl or pyranyl; or indolyl.

Favourably, Q represents pyridinyl.

An example of a substituent for Q is a nitro group, a halogen, a methylsulphonamide group or a 1-imidazo group.

In a preferred aspect, Q is phenyl or substituted phenyl, most preferably nitrophenyl such as 4-nitrophenyl.

Suitably, one or two of R_1, R_2 and R_3 represents alkoxy, for example methoxy or ethoxy, preferaby methoxy, the remaining member(s) being H.

Suitably, Ar represents a substituted or unsubstituted heteroaryl group, generally unsubstituted.

Preferably, Ar represents substituted or unsubstituted aryl, wherein the optional substituents are the above defined R_1, R_2 and R_3, especially alkoxy such as methoxy.

An example of Ar is alkoxy phenyl such as dimethoxyphenyl, in particular 3,4-dimethoxyphenyl.

As used herein, the term "alkyl" includes straight or branched chain alkyl groups having from 1 to 12, favourably 1 to 6, carbon atoms and shall include such alkyl groups when forming part of other groups such as alkoxy or arylalkyl groups.

As used herein, the term "alkenyl" includes straight or branched chain alkylene groups having from 2 to 12, favourably 2 to 6, carbon atoms and one or more double bonds.

As used herein, the term "alkynyl" includes straight or branched chain alkynlene groups having from 2 to 12, favourably 2 to 6, carbon atoms and one or more triple bonds.

As used herein the term "aryl" includes phenyl and naphthyl, preferably phenyl.

Unless otherwise specified, optional substituents for aryl include up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy or alkylcarbonyl groups.

Suitable heteroaryl groups include substituted or unsubstituted, single or fused ring heteroaryl groups having 5 or 6 ring atoms which comprise up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

In particular, the heteraryl group comprises 1, 2 or 3 heteroatoms, in each ring especially 1 or 2, selected from oxygen, sulphur or nitrogen.

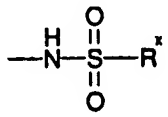
Suitable heteroaryl groups include benzo fused 5 or 6 membered hetero ring, such as indole, benzofuran and benzothiophene groups.

Suitable substituents for the heteroaryl group include the substituents as described herein with regard to the aryl group.

As used herein, the term "cycloalkyl" includes cyclic alkyl carbon-carbon linkages of four to seven carbon atoms.

As used herein "halogen" includes fluorine, chlorine or bromine.

As used herein, the term "alkylsulfonamido" includes a radical of the formula



wherein R^x is an alkyl group.

As used herein, the term "cardiac arrhythmia" relates to any variation from the normal rhythm of heart beat, including, without limitation, sinus arrhythmia, premature heartbeat, heartblock, fibrillation, flutter, tachycardia, paroxysmal tachycardia and premature ventricular contractions.

The compounds of formula (I) may possess a chiral carbon atom (for example when B represents a branched alkylene group) and it may therefore exist in more than one stereoisomeric form. The invention extends to any of the stereoisomeric forms, including enantiomers of the compounds of formula (I) and to mixtures thereof, including racemates. The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

The pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts with pharmaceutically acceptable mineral acids such as

hydrochloric, hydrobromic, boric, phosphoric, sulphuric and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto-glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids. Preferably the acid addition salt is a hydrochloride.

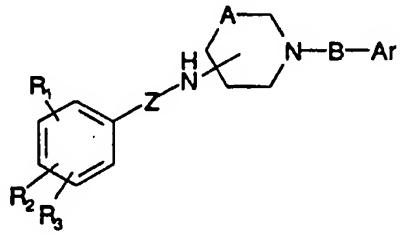
Pharmaceutically acceptable salts also include quaternary salts. Examples of quaternary salts include such compounds quaternised by compounds such as R^y-T wherein R^y is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R^y include methyl, ethyl and *n*- and *iso*- propyl; and benzyl and phenethyl. Suitably T includes halide such as chloride, bromide and iodide.

Pharmaceutically acceptable salts also include pharmaceutically acceptable N-oxides, and the invention extends to these.

The compounds of the formula (I) and their salts may also form solvates, especially pharmaceutically acceptable solvates, such as hydrates, and the invention extends to these, and especially to the pharmaceutically acceptable solvates.

The salts of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form an aspect of the present invention.

A compound of formula (I) or a salt thereof, or a solvate thereof, may be prepared by reacting a compound of formula (II):



(II)

wherein A, B, Z, R_1, R_2, R_3 and Ar are as defined in relation to formula (I) with a reagent of formula (III);

$$QL^1$$

(III)

wherein Q is as defined in relation to formula (I) and (a) for compounds of formula (I) wherein D is CO or SO_2, L^1 represents COX or SO_2X respectively and wherein X is a leaving group such as a halogen, and (b) for compounds of formula (I) wherein D

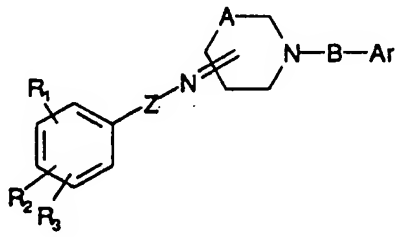
is NHCO, L^1 is N=C=O; and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

The reaction conditions for the reaction between compounds of formulae (II) and (III) are conventional conditions appropriate to the nature of the reagent used, generally however the reaction may be carried out in an inert solvent, such as methylene chloride, at any suitable temperature providing a convenient rate of formation of the desired product, generally at an ambient to elevated temperature, conveniently at the reflux temperature of the solvent and preferably in the presence of a base such as triethylamine.

The compounds of formula (II) may be prepared by reducing a compound of formula (IV)

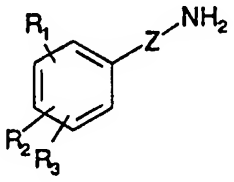


(IV)

wherein A, B, Z, R_1, R_2, R_3 and Ar are as defined in relation to formula (I).

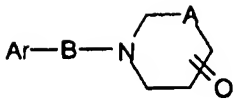
The reduction of the compound of formula (III) may be effected using any appropriate reduction method, for example metal hydride reduction using a lithium hydride such as lithium aluminium hydride in an aprotic solvent such as tetrahydrofuran (THF), at any suitable temperature which provides a convenient rate of reaction, generally at ambient to an elevated temperature, conveniently at ambient temperature.

A compound of formula (IV) may be prepared by reacting a compound of formula (V):



(V)

wherein Z, R_1, R_2 and R_3 are as defined in relation to formula (IV), with a compound of formula (VI):

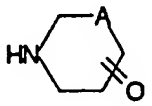


(VI)

wherein A, B and Ar are as defined in relation to the compound of formula (IV).

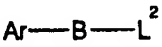
The reaction between the compounds of formulae (V) and (VI) may be carried out in a solvent such as toluene, at any suitable temperature providing a convenient rate of formation of the desired product, generally at an elevated temperature and conveniently at the reflux temperature of the solvent; the water produced in the reaction is removed by any conventional means, for example by means of a Dean and Stark apparatus.

A compound of formula (VI) may be prepared by reacting a compound of formula (VII):



(VII)

wherein A is as defined in relation to formula (IV), with a compound of formula (VIII):



(VIII)

wherein B and Ar are as defined in relation to the compound of formula (VI) and L^2 represents a leaving group, such as halide, especially chloride, or a mesylate.

The reaction between the compounds of formulae (VII) and (VIII) may suitably be carried out in an aprotic solvent such as acetonitrile, at any suitable temperature providing a convenient rate of formation of the desired product, generally at an elevated temperature and conveniently at the reflux temperature of the solvent; preferably the reaction is carried out in the presence of a base such as potassium carbonate.

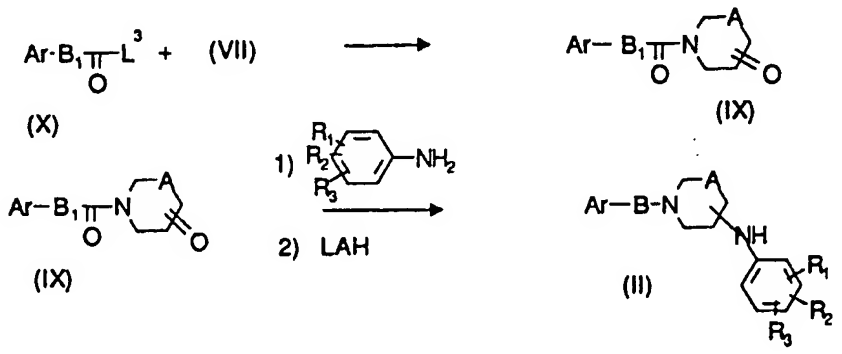
The compounds of formulae (VII) are known commercially available compounds and may also be prepared according to known procedures such as those described in .Belstein, Vol 21, Ist Edition, page 262.

The compounds of formulae (VIII) are known compounds and may be prepared according to known procedures such as those to described in Chemical Abstracts 78: P 84279n.

The compounds of formula (II) may also be prepared using analogous procedures to those described in European Patent Application, Publication Number 0416581.

A compound of formula (II), wherein Z represents a bond, may also be obtained by the methods illustrated in Scheme I.

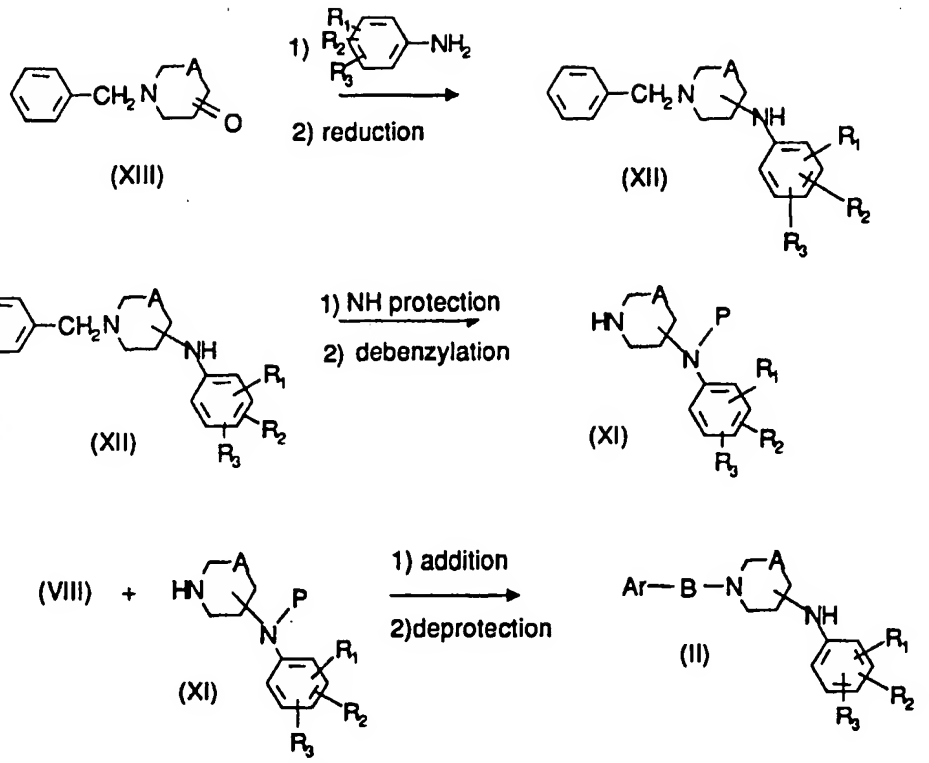
Scheme I



wherein A, Ar, B, R_1, R_2 and R_3 are as defined in relation to formula (I), B_1 represents C_{2-3} alkylene and L_3 represents a halide such as chloride or bromide.

A compound of formula (II), wherein Z represents a bond, may also be obtained starting from N-benzyl-4-oxo piperidine as illustrated in Scheme II

Scheme II



wherein A, Ar, B, R_1, R_2 and R_3 are as defined in relation to formula (I) and P represents a protecting group such as an acyl group, for example an acetyl group.

The insertion and removal of P may be achieved in the conventional manner depending upon the nature of the protecting group used. Also the debenzylation can be achieved by conventional means, for example with hydrogen in the presence of a catalyst like palladium on charcoal.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: The present invention accordingly provides a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

More particularly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders.

A compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

A compound of formula (I) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof is normally administered in unit dosage form.

An amount effective to treat the disorder hereinbefore described depends upon such factors as the efficacy of a compound of formula (I) , the particular nature of the pharmaceutically acceptable salt or pharmaceutically acceptable solvate chosen, the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 500 mg for example 2 to 50 mg, of the compound of the invention. Unit doses will normally be administered once or more than once a day, for example 2,3,4,5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 2500 mg, more usually 50 to 2000 mg, for example 10 to 75mg, that is in the range of approximately 0.002 to 35 mg/kg/day, more usually 1 to 30 mg/kg/day, for example 0.15 to 1 mg/kg/day.

At the above described dosage range, no toxicological effects are indicated for the compounds of the invention.

In such treatment, the compound may be administered by any suitable route, e.g. by the oral, parenteral or topical routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a human or veterinary pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

For topical administration, the composition may be in the form of a transdermal ointment or patch for systemic delivery of the compound and may be prepared in a conventional manner, for example, as described in the standard textbooks such as 'Dermatological Formulations' - B.W. Barry (Drugs and the Pharmaceutical Sciences - Dekker) or Harrys Cosmeticology (Leonard Hill Books).

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of arrhythmia and/or ischaemic arrhythmia disorders the compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in an amount in the range of from 0.01 mg/kg to 15 mg/kg, for example 0.1 mg/kg to 5 mg/kg, such that the total daily dose for a 70 kg adult will generally be in the range of from 0.7 to 6300 mg, and more usually about 7 to 2100 mg.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

In a further aspect the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders.

The following Descriptions and Examples illustrate the invention but do not limit it in any way.

Description 1 2-(3,4-Dimethoxyphenyl)ethyl methanesulfonate

To a mixture of 2-(3,4-dimethoxyphenyl)ethyl alcohol (18.2 g, 100 mmol) and triethylamine (10.1 g, 100 mmol) in 300 ml of acetonitrile was added dropwise (over 30-min period) methane sulfonyl chloride (11.5 g, 100 mmol) in such a way to maintain inner temperature below 40°C. The reaction mixture was allowed to stand at room temperature overnight. The resulting mixture was filtrated over a pad of celite. The filtrate was concentrated *in vacuo*. The crude product was dissolved in 200 ml of ethyl acetate, washed twice with 100 ml of water, dried over magnesium sulfate, and concentrated *in vacuo*. 22 g of the title compound was isolated and used without further purification.

oil

IR(NaCl cell) : ν = 2,950 ; 2,825 ; 1,600; 1,510 ; 1,470 ; 1,350 ; 1,270 ; 1,175 ; 1,025 cm^{-1}

^1H NMR ($CDCl_3$) : δ = 2.85 (s,3H,$\underline{CH_3}S$); 3.00 (t,2H,J=7Hz,$\underline{CH_2}Ph$) ; 3.86 (s,3H,$\underline{CH_3}OPh$); 3.88 (s,3H,$\underline{CH_3}OPh$); 4.40 (t,2H,J=7Hz,$\underline{CH_2}O$) ; 6.75-6.85 (m,3H,Ar) ppm.

Description 2 1-[2-(3,4-Dimethoxyphenyl)ethyl]4-piperidinone

A mixture of 2-(3,4-dimethoxyphenyl)ethyl methanesulfonate (22 g, 85 mmol), 4-piperidinone monohydrate hydrochloride (13 g, 85 mmol), and potassium carbonate (23.5 g, 170 mmol) in 200 ml of acetonitrile was refluxed and stirred for 24 hours. The reaction mixture was concentrated *in vacuo* to dryness. The resulting crude product was successively dissolved in 200 ml of ethyl acetate, washed three times with 100 ml of water, dried over magnesium sulfate, and concentrated *in vacuo*. 15 g of the title compound was isolated after trituration with isopropyl ether and drying *in vacuo*.

m.p = 81°C

IR(KBr) : ν = 2,925 ; 2,825 ; 2,775; 1,720 ; 1,590 ; 1,520 ; 1,270 ; 1,230 ; 1,160; 1,020 cm^{-1}

^1H NMR ($CDCl_3$) : δ = 2.40-2.55 (m,4H,$\underline{CH_2}CO\underline{CH_2}$); 2.65-2.90 (m,8H,$\underline{CH_2}N\underline{CH_2}$,Ph$\underline{CH_2}\underline{CH_2}$N); 3.86 (s,3H,$\underline{CH_3}OPh$); 3.88 (s,3H,$\underline{CH_3}OPh$); 6.70-6.85(m,3H,Ar) ppm.

Description 3 N-(3,4-Dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinamine

A mixture of 1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinone (10 g, 38 mmol) and (3,4-dimethoxy)benzeneamine (5.85 g, 38 mmol) in 150 ml of toluene was refluxed for 4 hours, using a Dean and Stark apparatus for removing water. After cooling to

room temperature, the reaction mixture was concentrated *in vacuo* to dryness. The resulting crude product was dissolved in 200 ml of anhydrous THF. Lithium aluminium hydride (2.9 g, 76 mmol) was added within 5 min. The reaction mixture was stirred at room temperature overnight. After cooling with a ice bath, the reaction mixture was quenched by successively 2.9 ml of water, 2.9 ml of 15% aqueous NaOH, and 8.7 ml of water. The inorganic compound was removed by filtration and washed with 50 ml of ethyl acetate. The filtrate was concentrated *in vacuo*. The resulting crude product was dissolved in 200 ml of ethyl acetate and successively washed twice with 100 ml of water, dried over magnesium sulfate, concentrated *in vacuo* to dryness, and triturated with 20 ml of ethyl ether. 8.75 g of the title compound was isolated after filtration and drying *in vacuo*.

m.p = 101°C

IR(KBr) : ν = 3,375; 2,950; 2,830; 1,590; 1,520; 1,260; 1,240; 1,020 cm^{-1}

^1H NMR (DMSO-d_6) : δ= 1.33 (m,q-like,2H,J=10Hz,CH_2CHCH_2); 1.89 (m,d-like, 2H, J=10Hz,CH_2CHCH_2); 2.11 (m,t-like,2H,J=10.5Hz,$PhCH_2$); 2.40-2.55 (m,2H,CH_2N); 2.60-2.65 (m,2H,CH_2N); 2.80-3.00 (m,2H,$PhCH_2CH_2N$); 3.05-3.20 (m,7H,-CHN); 3.61 (s,3H,OCH_3); 3.68 (s,3H,OCH_3); 3.71 (s,3H,OCH_3); 3.73 (s,3H,OCH_3); 5.02 (d,1H,J=7Hz,exch D_2O,NH); 6.05 (dd,1H,J=8.5Hz,Ar); 6.27 (d,1H,Ar); 6.65-6.90 (m,4H,Ar) ppm.

Description 4 N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinamine.

Reacting 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidone (D2) with 2-(3,4-dimethoxyphenyl)ethylamine using a procedure similar to that described in description 3 afforded the title compound. m.p.235°C.

Description 5 1-[2-(1H-indol-3-yl)ethyl]-4-piperidone

Reacting methyl 1H-indol-3-ethanesulfonate with 4-piperidone monohydrate hydrochloride, using the same procedure as described in description 2 provided the title compound

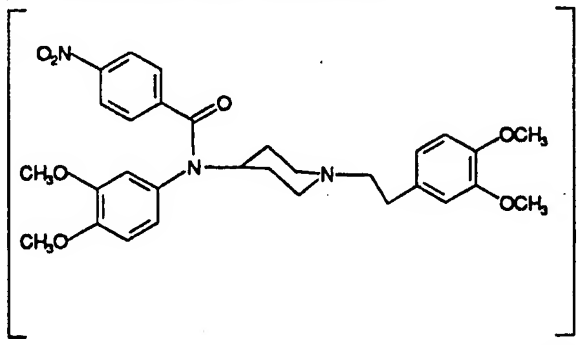
m.p. 135°C.

Description 6 1-[2-(1H-indol-3-yl)ethyl]-N-(3,4-dimethoxyphenyl)-4-piperidinamine.

Reacting 1-[2-(1H-indol-3-yl)ethyl]-4-piperidone (D5) with (3,4-dimethoxy)benzeneamine, using the same procedure as described in description 3 provided the title compound.

m.p. 95°C.

Example 1 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinyl]-4-nitrobenzamide hydrochloride



.HCl

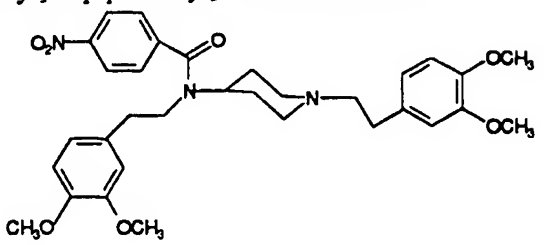
To a mixture of N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (1.14 g, 2.8 mmol) and triethylamine (0.5 g, 5 mmol) in 20 ml of chloroform, was added a solution of 4-nitrobenzoyl chloride (0.9 g, 5 mmol) in 10 ml of chloroform. The reaction mixture was stirred at room temperature for 2 hours, then refluxed for 2 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The resulting crude product was dissolved in 50 ml of 0.5 N aqueous HCl. The aqueous layer was separated and successively washed with 10 ml of ethyl acetate, treated with 1 N aqueous NaOH, and extracted with 50 ml of ethyl acetate. The organic layer was separated, washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. The obtained crude product was purified by flash chromatography (silica gel, CH_2Cl_2 : MeOH 98:2 as eluent). 0.31 g of a pure compound was isolated after crystallisation in acetonitrile. This compound was dissolved in 2 ml of ethyl alcohol and 20 ml of ethyl ether and treated carefully with a solution of hydrochloric acid in ethyl ether. 0.3 g of the title compound was isolated after filtration and drying *in vacuo*.

m.p around 160°C (amorphous solid)

IR(KBr): ν = 3,450; 2,950; 2,850; 2,525; 1,640; 1,590; 1,520; 1,350; 1,270; 1,240; 1,025 cm^{-1}

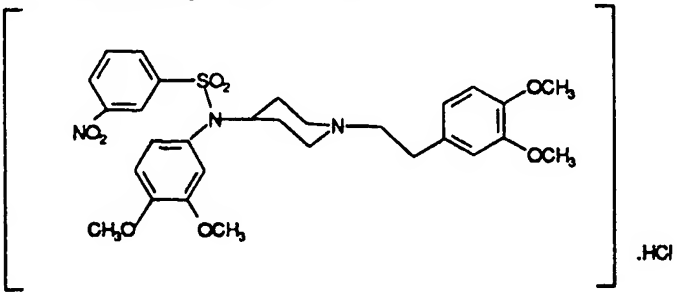
^1H NMR (DMSO-d_6) : δ = 1.70-1.95 (m,2H,$C\underline{H}_2$-$CHCH_2$); 2.00-2.25 (m,2H,$C\underline{H}_2$-$CHCH_2$); 2.80-3.00 (m,2H,$C\underline{H}_2Ph$); 3.05-3.30 (m,4H,$C\underline{H}_2NC\underline{H}_2$); 3.50-3.80 (m,14H,$(CH_3O)$x4,$PhCH_2C\underline{H}_2N$); 4.70-4.90 (m,1H,-C$\underline{H}$N); 6.65-7.00 (m,6H,Ar); 7.56 (d,2H,J=8Hz,Ar); 8.06 (d,2H,J=8Hz,Ar); 9.65 (m,1H,exch D_2O,N$\underline{H}$) ppm.

Example 2 N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-nitrobenzamide



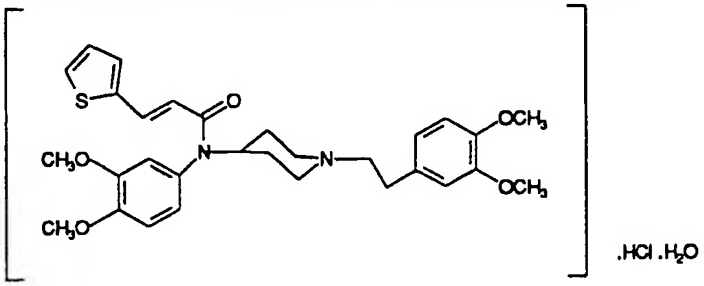
Reacting N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinamine (D4) with 4-nitrobenzoyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 80°C.

Example 3 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-3-nitrobenzenesulphonamide, hydrochloride



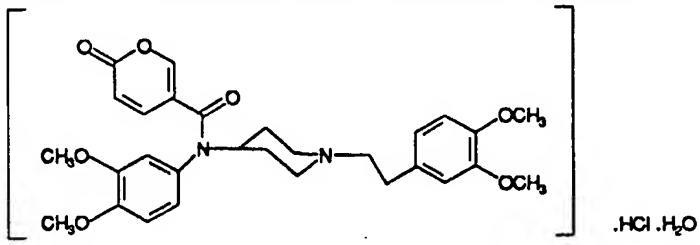
Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinamine (D3) with 3-nitrobenzenesulfonyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 218°C.

Example 4 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-3-(2-thiophenyl)-2-propenamide, hydrochloride, hydrate



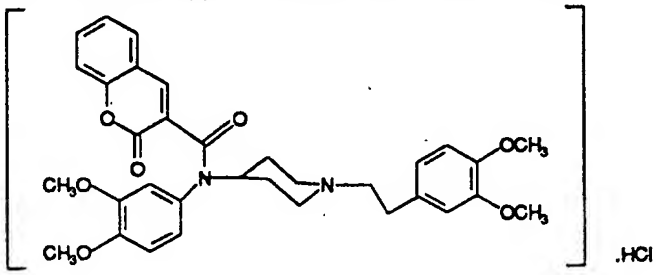
Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 3-(2-thienyl)-propenoyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 165°C.

Example 5 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-6-oxo-6H-3-pyrancarboxamide, hydrochloride, hydrate



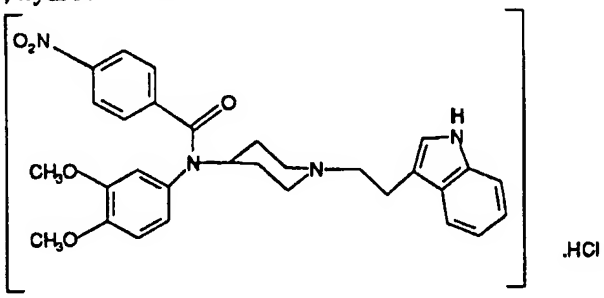
Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 2-oxo-2H-pyran-5-carbonyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 190°C.

Example 6 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-2-oxo-2H-3-benzopyrancarboxamide, hydrochloride



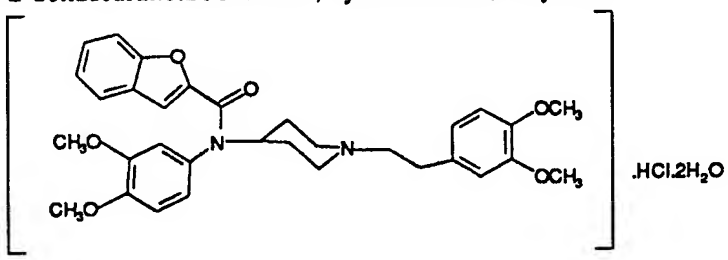
Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 2-oxo-2H-benzopyran-3-carbonyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 230°C.

Example 7 N-[1-[2-(1H-Indol-3-yl)ethyl]-4-piperidinyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide, hydrochloride



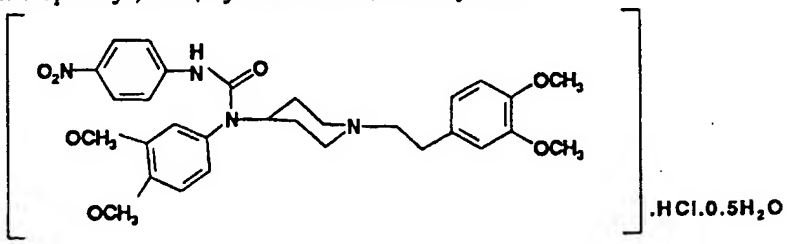
Reacting 1-[2-(1H-indol-3-yl)ethyl]-N-(3,4-dimethoxyphenyl)-4-piperidinamine (D6) with 4-nitrobenzoyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 290°C.

Example 8 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-2-benzofurancarboxamide, hydrochloride, dihydrate



Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with benzofuran-2-carbonyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p.130°C.

Example 9 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-N'-(4-nitrophenyl)urea, hydrochloride, hemihydrate



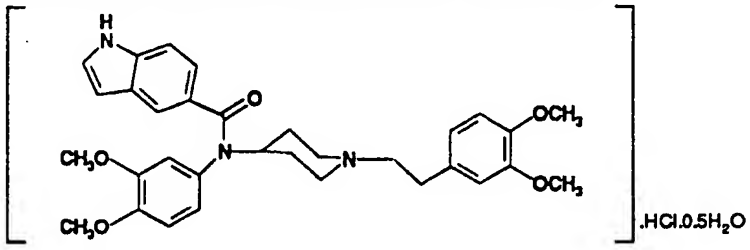
A mixture of N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinamine (D3)(1g, 2.5 mmol), 4-nitro-isocyanatobenzene (0.41g, 2.5 mmol)

and triethylamine (0.5g, 5 mmol) in 20ml of chloroform is stirred over night. The solvent is concentrated *in vacuo*. The residue is taken up in 50 ml of ethyl acetate, washed three times with water, dried over magnesium sulfate, and concentrated *in vacuo*. The obtained crude product was purified by chromatography (silica gel, ethyl acetate) to provide the title compound as the free base.

The compound was then dissolved in a small amount of acetonitrile and treated by a solution of anhydrous hydrochloric acid in ethyl ether. 0.32g of the title compound was isolated after filtration and drying *in vacuo*.

m.p. 220°C.

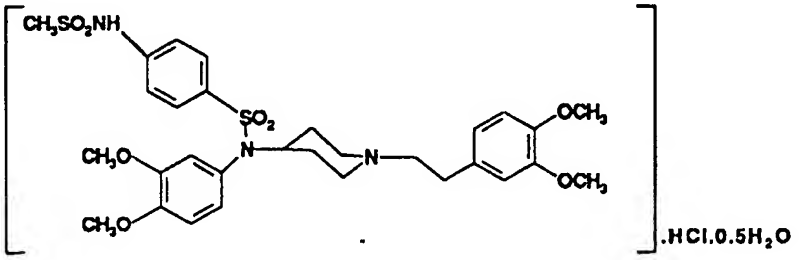
Example 10 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-5-indolecarboxamide, hydrochloride, hemihydrate



Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 1H-indol-5-carbonyl chloride using a procedure similar to that described in example 1 provided the title compound.

m.p. 160°C.

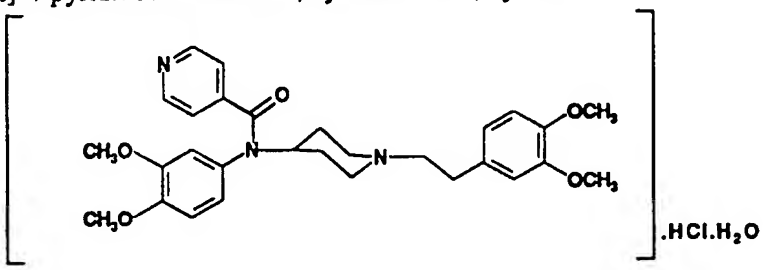
Example 11 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-(methylsulphonylamine)benzenesulphonamide, hydrochloride, hemihydrate



Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 4-(methylsulfonylamino)benzenesulfonyl chloride using a procedure similar to that described in example 1 provided the title compound.

m.p – 120°C

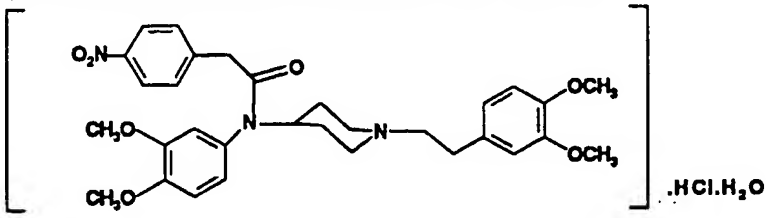
Example 12 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-pyridinecarboxamide, hydrochloride, hydrate



Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 4-pyridinecarbonyl chloride using a procedure similar to that described in example 1 provided the title compound.

m.p. ~ 160°C

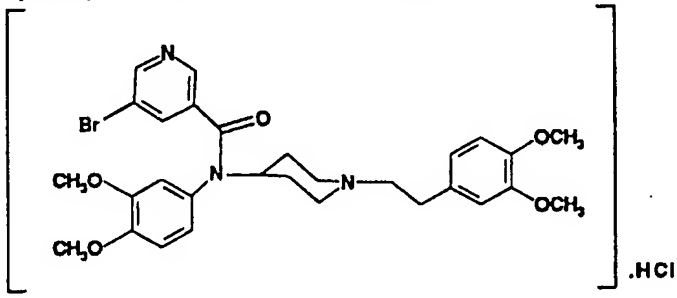
Example 13 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-nitrobenzeneacetamide, hydrochloride, hydrate



Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 4-nitrobenzeneacetyl chloride using a procedure similar to that described in example 1 provided the title compound.

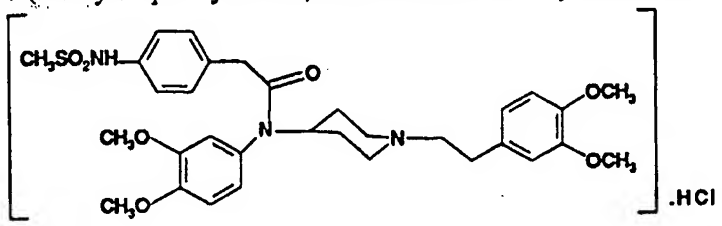
m.p. 131°C

Example 14 5-Bromo-N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-3-pyridinecarboxamide, hydrochloride



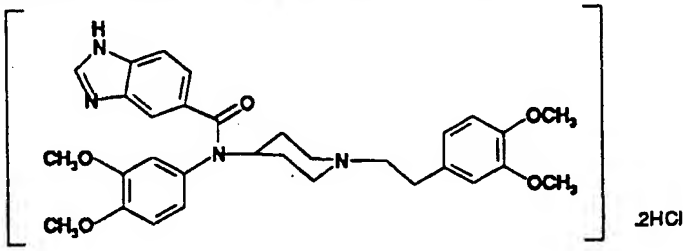
Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 5-bromo-3-pyridinecarbonyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 126°C

Example 15 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-(methylsulphonylamino)benzeneacetamide, hydrochloride



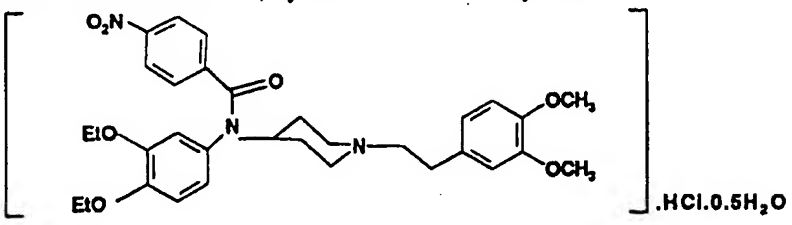
Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 4-(methylsulfonylamino)benzeneacetyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 200-205°C

Example 16 N-(3,4-Dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-1H-benzimidazole-5-carboxamide, dihydrochloride



Reacting N-(3,4-dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 1H-benzimidazole-5-carbonyl chloride using a procedure similar to that described in example 1 provided the title compound.
m.p. 200°C.

Example 17 N-(3,4-Diethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-nitrobenzenecarboxamide, hydrochloride, hemihydrate



Reacting N-(3,4-diethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinamine (D3) with 4-nitrobenzoyl chloride using a procedure similar to that described in example 1 provided the title compound.

m.p. – 110°C

Pharmacological data

Methodology

Guinea pigs (300-350 g) were anesthetized by intravenous injection of sodium pentobarbital (60 mg/kg). After thoracotomy the heart was rapidly excised and placed in oxygenated Tyrode solution. Papillary muscles were removed from the right ventricle. Preparations were then fixed to the silastic base of a 5 ml organ bath and superfused with oxygenated Tyrode solution maintained at 37 ± 1°C.

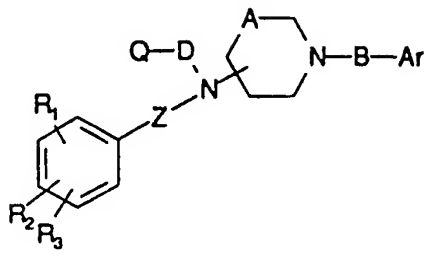
The modified Tyrode solution (pH 7.35) contained the following (mM) : NaCl 125, KCl 4.0, $MgCl_2$ 0.5, $CaCl_2$ 1.8, $NaHCO_3$ 24, NaH_2PO_4 0.9 and glucose 5.5. The solution was equilibrated with a gas mixture of 95% O_2 - 5% CO_2.

After a stabilisation period (at least 1h), transmembrane action potentials were recorded with conventional microelectrodes (10 MOhm) connected to a high input impedance amplifier (BIOLOGIC VF 180). External stimuli were delivered to the preparation with bipolar platinum electrodes placed at one end of the muscle. The pulse duration was 1 ms and the amplitude was twice threshold. The basic cycle length was 1000 ms (PULSAR 6i stimulator). The signals were monitored on a storage oscilloscope (GOULD 1602) and simultaneously recorded on a digital tape recorder (BIOLOGIC DTR 1200) for further analysis.

Measurements were made of action potential amplitude (APA) and action potential durations at 30 and 90% repolarization (APD30 and APD90 respectively). Recordings were made after 30 min of equilibration for each concentration. Only recordings in which the same impalement was maintained throughout the entire experiment were used for analysis.

Claims:

1. A compound of formula (I) :



(I)

or a salt thereof, or a solvate thereof, wherein

A represents $(CH_2)_n$ wherein n represents zero or an integer 1 or 2;

B represents a C_{2-4} n-alkylene group wherein each carbon is optionally substituted by a C_{1-6} alkyl group;

Z represents a bond $(CH_2)_m$ wherein m is an integer in the range of form 1 to 4 or X-CH_2-CH_2 wherein X represents O or S;

D represents CO, SO_2, NH-CO, NH-SO_2, -CH=CH- or P(O)OR_4 wherein R_4 is C_{1-6} alkyl;

Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamide, 1-imidazo, alkyl or haloalkyl, or Q represents substituted furanyl, substituted thienyl or substituted or unsubstituted: pyranyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl, indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group;

R_1, R_2 and R_3 each independently represent H, alkyl, OH or alkoxy or, if attached to adjacent carbon atoms, any two of R_1, R_2 or R_3 together with the carbon atoms to which they are attached may form a fused heterocyclic ring of four to six atoms wherein one, two or three of the said atoms are oxygen or nitrogen; and

Ar represents substituted or unsubstituted aryl, wherein the optional substituents are the above defined R_1, R_2 and R_3 or Ar represents a substituted or unsubstituted heteroaryl group.

2. A compound according to claim 1, wherein Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamido, 1-imidazo, alkyl or haloalkyl.

3. A compound according to claim 1 or claim 2, wherein Q represents substituted aryl.

4. A compound according to any one of claims 1 to 3, wherein Q represents nitro phenyl.

5. A compound according to any one of claims 1 to 4, wherein D represents CO, SO_2, NH-CO or -CH=CH-.

6. A compound according to any one of claims 1 to 5, wherein D represents CO.

7. A compound according to any one of claims 1 to 6, wherein A represents CH_2.

8. A compound according to any one of claims 1 to 7, wherein B represents represents CH_2CH_2.

9. A compound according to any one of claims 1 to 8, wherein Z represents a bond.

10. A compound according to any one of claims 1 to 9, wherein Ar represents 3,4-dimethoxyphenyl.

11. A compound according to claim 1, selected from the list consisting of:

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]4-piperidinyl]-4-nitrobenzamide,

N-[2-(3,4-dimethoxyphenyl)ethyl]-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-nitrobenzamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-3-nitrobenzenesulphonamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-3-(2-thiophenyl)-2-propenamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-6-oxo-6H-3-pyrancarboxamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-2-oxo-2H-3-benzopyrancarboxamide,

N-[1-[2-(1H-indol-3-yl)ethyl]-4-piperidinyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-2-benzofurancarboxamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-N'-(4-nitrophenyl)urea,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-5-indolecarboxamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-(methylsulphonylamine)benzenesulphonamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-pyridinecarboxamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-nitrobenzeneacetamide,

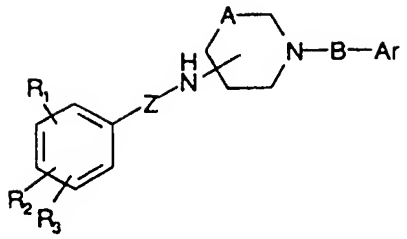
5-bromo-N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-3-pyridinecarboxamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-(methylsulphonylamino)benzeneacetamide,

N-(3,4-dimethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-1H-benzimidazole-5-carboxamide, and

N-(3,4-diethoxyphenyl)-N-[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]-4-nitrobenzenecarboxamide; or a salt thereof, or a solvate thereof.

12. A process for preparing a compound of formula (I) as defined in claim 1, or a salt thereof, or a solvate thereof, which process is characterised by reacting a compound of formula (II):



(II)

wherein A, B, Z, R_1, R_2, R_3 and Ar are as defined in relation to formula (I) with a reagent of formula (III);

$$QL^1$$

(III)

wherein Q is as defined in relation to formula (I) and (a) for compounds of formula (I) wherein D is CO or SO_2, L^1 represents COX or SO_2X respectively and wherein X is a leaving group such as a halogen, and (b) for compounds of formula (I) wherein D is NHCO, L^1 is N=C=O; and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

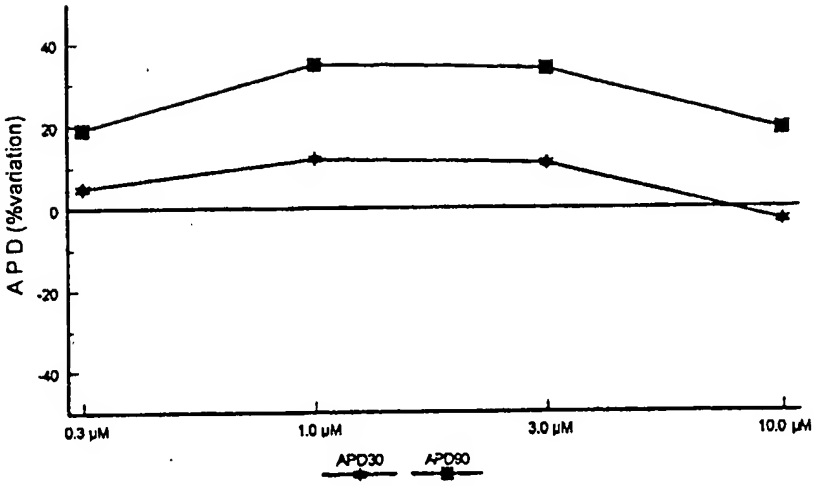
13. A pharmaceutical composition comprising a compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

14. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

15. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of arrhythmia.

16. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of arrhythmia and ischaemic rhythm disorders.

17. A method for the treatment and/or prophylaxis of arrhythmia and ischaemic rhythm disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.



Effect of compound of example 1 on action potential duration (APD) recorded in guinea-pig papillary muscle. Action potential duration was measured at 30% (APD30) and 90% (APD90) of repolarization.

INTERNATIONAL SEARCH REPORT

Inte. ›nal Application No
PCT/EP 94/01704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D211/58 C07D401/06 C07D401/12 C07D405/12 C07D417/12
A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 160 422 (BOC) 6 November 1985 see page 36, line 12 - line 13 see page 40, line 9 - line 12 see page 42, line 1; claims 1,5 ---	1,2,5-9, 13,14
A	EP,A,0 379 441 (RHONE-POULENC SANTE) 25 July 1990 see page 10, line 55 - page 11, line 28; claims 1,2,5,13; examples 4-9,16,21-23 ---	1-17
A	EP,A,0 416 581 (G.D. SEARLE & CO.) 13 March 1991 cited in the application see claims; examples --- -/--	1-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 1994	20. 09. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (› 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (› 31-70) 340-3016	Zervas, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intc onal Application No
PCT/EP 94/01704

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 196 210 (STEFAN SANCZUK ET AL.) 1 April 1980 see claims; examples	1-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/01704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 17 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.: 1-10 and 12-17 (searched incompletely)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The definiton of the substituents is too general and/or encompasses too broad a range of totally different chemical groups, only partially supported by the examples given in the descriptive part of the application. Guided by the spirit of the application and the descriptive part of the present application the search has been based on the examples (cf. Art. 6 PCT)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/EP 94/01704

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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